Clin Exp Allergy 2003; **33**:1471–1475

EDITORIAL

Active cigarette smoking and asthma

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Introduction

Active cigarette smoking is common in adult asthmatic patients and prevalence rates are similar to the general population. Current smoking rates among asthmatic patients range from 17% to 35% [1–7]. The highest rates are found in adults presenting to hospital emergency departments with acute asthma [3]. An additional number of adult asthmatics are former smokers with prevalence rates ranging from 22% to 43% [1, 2]. The large subgroup of adult asthmatics who are cigarette smokers has been excluded from many studies presumably because investigators were concerned that patients with smoking-related chronic obstructive pulmonary disease (COPD) might be included in the study population. Thus, there is relatively little published information on the influence of current cigarette smoking on asthma morbidity, therapeutic response to asthma medications and mechanisms of disease. In this edition of the journal, Sunyer et al. [8] examined the effects of asthma on peripheral cell blood counts among smokers and non-smokers and their results suggest that smoking modifies the immunological response in asthma. In this editorial we will assess this new data in the light of what is known about the clinical and immunological effects of active smoking in adults with asthma (Fig. 1).

Clinical effects of active smoking

The morbidity and mortality from asthma are increased in individuals who are cigarette smokers [1–5, 9–12]. Current asthmatic smokers have more severe asthma symptoms [1, 2] and worse indices of health status when compared with never smokers [4]. Cigarette smoking and asthma combine to accelerate the decline in lung function to a greater degree than either factor alone [7, 13]. Current smoking is associated with less appropriate management of asthma exacerbations, increased hospital-based care for asthma and more emergency department visits [3, 4, 10, 11]. The 6-year mortality rates are higher for smokers than non-smokers following a near-fatal asthma attack, with an age adjusted odd ratio of 3.6 [12], although there is conflicting evidence as to whether current smoking is a risk factor for near fatal asthma [5, 9].

Therapeutic response to corticosteroids

Corticosteroids are the most effective anti-inflammatory therapy for chronic asthma. Both national and international asthma guidelines emphasize the importance of the early introduction of inhaled corticosteroids as first-line therapy for those with mild disease [14, 15]. The evidence for these recommendations is based on clinical trials that have been undertaken largely in asthmatic patients who are never smokers or former smokers. Until recently there was little information about the effect of active smoking on corticosteroid therapy in asthma. Active cigarette smoking impairs the efficacy of short-term inhaled corticosteroid treatment in steroid-naïve asthmatic patients [16]. In this randomized placebo-controlled study, the effect of treatment with inhaled fluticasone propionate, 1000 μg daily, or placebo for 3 weeks was studied in steroid-naïve adult asthmatic patients. Non-smokers had a significant increase in mean morning peak expiratory flow (PEF), mean forced expiratory volume in 1 s (FEV_1) and geometric mean PC_{20} to methacholine and a significant decrease in sputum eosinophils following fluticasone compared to placebo. No significant changes were observed in the smoking asthmatics for any of these parameters. This result confirmed an earlier uncontrolled study that reported a reduced response to inhaled corticosteroids in terms of airway function in asthmatic smokers compared to non-smokers [17]. It remains to be established whether inhaled corticosteroid therapy, when administered for a longer duration, has beneficial effects on clinical end-points including exacerbation rates.

Active smoking also impairs the efficacy of short-term oral corticosteroid treatment in chronic stable asthma [18]. The effect of treatment with prednisolone 40 mg daily or placebo for 2 weeks was studied in a randomized controlled trial of asthmatic smokers, ex-smokers and never-smokers. All subjects had clinical asthma with evidence of reversibility in FEV_1 after nebulized salbutamol of 15% and a mean post-bronchodilator FEV_1% predicted >80%. There was a significant improvement following oral prednisolone compared to placebo in FEV_1, morning PEF and asthma control score in asthmatic never smokers but no change in asthmatic smokers.

Taken together the results of these studies suggest that asthmatic smokers are resistant to corticosteroids. The effect of smoking on asthma may be partially reversible, since former smokers show improvement in morning PEF values but not asthma symptom control scores following a short course of oral corticosteroid treatment [18]. Previous work on resistance to corticosteroids in asthmatic smokers recruited individuals with a smoking pack history of $\geqslant 10$ years [16, 18, 19] and it is unclear whether the response to corticosteroids is also decreased when the smoking history is of a lower intensity. Further studies are also required to determine whether corticosteroid responsiveness is regained following smoking cessation, and if so, how quickly the restoration of corticosteroid sensitivity occurs.

These findings may have important clinical implications for asthmatics who smoke and reinforce the need for smoking

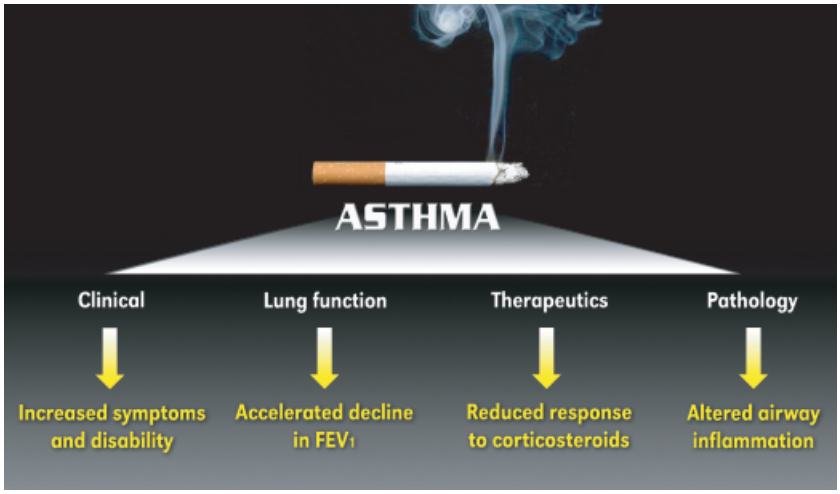

Fig. 1. Interaction of active cigarette smoking and asthma.

cessation in asthma, even in those with mild disease. Alternative or additional treatment to inhaled corticosteroids may be required for asthmatics who continue to smoke. Cigarette smoking causes a dose-related increase in urinary cysteinyl leukotriene E_4 production [20] and it would be of interest to examine the benefits on asthma control of leukotriene receptor antagonists in asthmatic smokers. Other therapies that would be worthy of study include long-acting β_2 receptor agonists [21] and phosphodiesterase-4 inhibitors [22].

Active smoking and inflammation in asthma

Circulating peripheral blood cells

In most but not all studies, current smoking is associated with increased circulating blood eosinophil counts in normal individuals [23–25] and asthma is also associated with raised circulating eosinophil counts [26]. In this edition of the journal, Sunyer et al. [8] report that circulating eosinophil counts are reduced in cigarette smokers with asthma compared with never-smokers with asthma, whereas the converse is true for non-asthmatic subjects. Circulating eosinophils, $CD4^+$ and $CD8^+$ T cell counts were measured in a cohort of HIV negative homosexual men ($n = 2194$), who were classified as having ($n = 197$) or not having asthma ($n = 1997$), based on a self-reported diagnosis of asthma. Data were collected semi-annually between 1987 and 1994 and the cohort remained HIV negative up to 2000. The odds ratio for circulating eosinophils being $\geqslant 4\%$ in asthma to non-asthma decreased from 2.7 (95% CI: 2.0, 3.6) to 1.5 (0.9, 2.3) in current smokers. Interestingly the odds ratio for ex-smokers was mid way between the figures for non-smokers and current smokers [2.1 (1.4, 3.1)]. In a small number of subjects ($n = 23$) who stopped smoking during the study, the proportion of circulating eosinophils increased in those with asthma, but fell in those who did not have asthma. Circulating peripheral blood T lymphocyte counts were similar in asthmatic smokers and non-smokers. There are several possible confounding factors that might influence the findings such as the study population of HIV-negative homosexual men, who have the potential to develop altered immune responses, and possible uncertainties about the accuracy of the diagnosis of asthma and lack of information on drug treatment in the different asthma groups. The main findings are likely, however, to be valid in view of the consistent trend in circulating eosinophil counts between the different subgroups of asthmatic patients. The results point to an altered circulating inflammatory cell response in the asthmatic smokers and in particular suppression of the increased circulating blood eosinophil count that is associated with asthma.

The reason(s) for the reduced circulating eosinophil counts in asthmatic smokers compared to non-smokers is not clear. Cigarette smoke might suppress increased eosinophil production from the bone marrow in asthma. However, in animal experiments chronic cigarette exposure stimulates rather than suppresses the bone marrow to release more immature polymorphonuclear leukocytes into the circulation [27]. Other possible mechanisms include increased rate of removal of eosinophils from the circulation into inflamed airways in asthmatic smokers compared to non-smokers or perhaps more likely increased apoptosis of activated eosinophils by the actions of exogenous nitric oxide in cigarette smoke [28, 29]. Currently, there is no direct evidence for these postulated mechanisms in asthma. Sunyer et al. [8] have suggested that atopy might influence the interaction between smoking and asthma. In the general population, current cigarette smoking is positively associated with specific IgE antibodies to house dust mite [30] and to the risk of developing occupational asthma due to IgE-inducing agents [31], whereas bronchial hyper-reactivity is reduced in atopic non-asthmatic individuals who smoke compared to non-atopic normal subjects [32]. Thus, it is possible that the atopic status of an asthmatic might influence the immunological effects of active smoking. Whatever the mechanism for the interaction of cigarette smoking and peripheral blood eosinophil counts in asthma, the observations of Sunyer et al. [8] raises an important issue of whether airway inflammation in cigarette smokers who have asthma differs from that of asthmatic non-smokers.

Airway inflammation

Cigarette smoking induces predominately a non-eosinophilic inflammation within the airways of non-asthmatic smokers

without airflow obstruction compared to non-smokers [33–36]. In central airways T lymphocytes and macrophages are increased within the airway wall and neutrophils are increased within bronchial secretions [33]. Peripheral airways show an inflammatory cell wall infiltration with mononuclear cells and with macrophages in the respiratory bronchioles [33]. A raised airway eosinophil count is not a feature of most studies of asymptomatic smokers [33–34] although peripheral lung sections from smokers compared with non-smokers have been reported to show increased numbers of eosinophils infiltrating the submucosa [37]. Another study reported a slightly higher induced sputum eosinophil count from asymptomatic smokers compared to non-smoking controls [38], although the values found in the smokers were within the normal range and the finding has not been confirmed by others [19, 39]. Repeated exposure to cigarette smoke induces eosinophilic airway inflammation and bronchial hyper-reactivity in guinea pigs, possibly secondary to platelet-activating factor release [40]. Cigarette smoke might also have secondary immunomodulatory effects on eosinophils through nicotine-mediated inhibition of release of pro-inflammatory cytokines from macrophages [41, 42].

Cigarette smoking may modify airway inflammation associated with asthma, although to date, there is limited data on the influence of active smoking on airway pathology in asthma. Using induced sputum to assess airway inflammation, Chalmers et al. [19] found reduced eosinophil counts in samples from asthmatic smokers compared to non-smokers. In addition, smoking was associated with neutrophilic airway inflammation and a relationship was found between smoking history, levels of sputum IL-8 and lung function. Cigarette smoking reduces exhaled nitric oxide in mild steroid-naïve asthmatic smokers compared with asthmatic non-smokers [43] and it is thought that cigarette smoke may inhibit inducible nitric oxide synthase either due to the direct feedback effect of the high concentration of nitric oxide within the cigarette smoke itself [30] or by the carbon monoxide in the cigarette smoke interacting with haem proteins [44]. IL-18 is a cytokine that is known to have an important role in the development of a Th1 lymphocyte responses. As such, it may have a regulatory role in asthma by inhibiting Th2 lymphocyte responses. Smoking significantly reduces IL-18 level in induced sputum and this effect is more pronounced in asthmatics than in normal subjects [45]. These findings suggest that cigarette smoking may, in part, modify airway inflammation by potentially altering the balance of Th1/Th2 cytokine secretion. Other pathways that might contribute to airway inflammation in asthmatic smokers include increased airway epithelial permeability [46], neurogenic inflammation [47] and oxidative stress [48]. Finally, airway remodelling might be more severe in asthmatic smokers as the airway longitudinal elastic fibre network is increased in non-fatal asthmatic smokers compared with non-smokers [49].

The findings from these studies taken together point to a combination of both heightened and suppressed inflammatory responses in asthmatic smokers compared with asthmatic non-smokers. Further studies using both invasive and non-invasive techniques are required to assess cellular and structural changes in the airways of asthmatic smokers compared with asthmatic non-smokers and COPD. In particular it will be important to establish whether the airway pathology of asthmatic smokers is predominantly that of asthmatic never-smokers, COPD or a combination of these two conditions.

Mechanisms of corticosteroid resistance in asthmatic smokers

Various different mechanisms have been implicated in corticosteroid resistance [50], but there have been no published studies in asthmatic smokers. Airway neutrophilia, which is found in asthmatics who have smoked for many years [19], is associated with a poor response to corticosteroids [51]. An increase in the number of glucocorticoid β receptors (GCR β) has been implicated as a mechanism for corticosteroid resistance [50, 52], and as neutrophils have a higher number of GCR β [53], this could account for the poor response to corticosteroids. Cigarette smokers have been shown to have an increase in the inflammatory cytokines IL-2 [54], IL-4 [55] and TNF-α [56], which have been implicated in corticosteroid resistance [57]. The precise mechanisms by which these cytokines might decrease corticosteroid responsiveness are unknown, but they have been reported to induce the expression of GCR β [53, 58]. NF-κ B has been associated with corticosteroid unresponsiveness in Crohn's disease [59], and it is possible that a similar mechanism exists in asthmatic smokers, as cigarette smoke contains bacterial lipopolysaccharide, an activator of NF-κB [60]. Finally, glucocorticoids require histone deacetylase (HDAC) activity for maximal suppression of cytokine induction [61], but smokers have decreased HDAC activity and this may lead to an increase in inflammatory gene expression and reduced sensitivity to corticosteroids [62].

Conclusions

Active cigarette smoking is common in adult asthmatic patients and is associated with increased morbidity from asthma and impaired short-term therapeutic responses to corticosteroids. Cigarette smoking may modify the inflammation associated with asthma, but information is limited on the influence of active cigarette smoking on airway pathology in asthma and on the mechanisms of corticosteroid resistance in asthmatic smokers. The effect of smoking cessation on these processes is also not clear, but the findings to date help reinforce the importance of smoking cessation in asthma. It is likely that alternative or additional therapies to inhaled corticosteroids are needed for asthmatic patients who are unable to stop smoking.

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